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REPLY BRIEF Address to: Box AF Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket	UCAL-269
	First Named Inventor	Prabhakara V. Choudary
	Application Number	09/425,075
	Filing Date	October 21, 1999
	Group Art Unit	1642
	Examiner Name	Larry Ronald Helms
	Title	*Functionally assembled antigen-specific intact recombinant antibody and a method for production thereof*

Sir:

This Reply Brief is in response to the Examiner's Answer mailed by the Office on May 3, 2004. This Reply Brief is accompanied by a Request for Oral Hearing.

Please any required fees to our Deposit Account No. 50-0815, order number UCAL-269.

REPLY BRIEF

In this Reply Brief, the Appellants address several assertions made by the Office in the Examiner's Answer (EA). Appellants note that all arguments presented in the prior Appeal Brief still apply with equal force, but are not reiterated here solely in the interest of brevity and for the convenience of the Board.

The claims recite a dual-expression cassette vector for antibody expression in *Pichia*. Claims 36-40 and 42-49 are rejected as obvious in view of Horwitz (PNAS 85:8678-8682, 1988) and further in view of Cregg (Developments in Industrial Microbiology 29:33-41, 1998); The Invitrogen Catalog (1997) (published 1/97, Yeast expression pages 14-19 and Master Catalog Amendment Notice for pPICZ vectors form 4/15/96); and Robinson (USPN 6,204,023). The basis for the rejection is as follows:

- Horwitz is cited for its disclosure of a *single* expression cassette vector system for production of functional antibodies in *S. cerevisiae*.
- Cregg is cited for its disclosure of a *Pichia* alcohol oxidase promoter.
- The Invitrogen Catalog is cited for its disclosure of a *single* expression cassette vector system for use in *Pichia*.
- Robinson is cited for its disclosure of a *dual* expression cassette system for producing functional antibodies in mammalian cells, and for its asserted suggestion that such a dual expression cassette system could be used for antibody production in "yeast".

Claims 36-40 and 41-49 are rejected based on a combination of these same references with Vanderlaan (USPN 5,429,925), which is cited for its disclosure of an anti-dioxin antibody.

In the Examiner's Answer, the Office reiterates its position that motivation to use Robinson's dual expression cassette vector to produce an antibody in *Pichia* is found in Horwitz, Cregg, and the Invitrogen catalog. (Examiner's Answer, paragraph bridging pages 5 and 6) The

Office has taken the position that Horwitz, Cregg, and the Invitrogen catalog essentially point towards *Pichia* as a system for high level expression of proteins. The element lacking in this combination, however, is the use of a dual expression cassette which provides for expression of the heavy chain polypeptide and the light chain polypeptide of the antibody from the same construct.

The Office has filled in this gap by relying on the disclosure of Robinson. The Office has repeatedly argued that Robinson discloses the use of a dual expression cassette vector for antibody expression in "yeast", where the Office – *despite Appellant's evidentiary support to the contrary* -- has interpreted the term "yeast", as used in Robinson, to refer to a genus of fungal species that encompasses *Pichia*. After concluding that "yeast" in Robinson means a genus of fungal species that encompasses *Pichia*, the Office argues that Robinson's disclosure, combined with the teachings of Cregg and the Invitrogen catalog, would motivate one of skill in the art to use a dual expression cassette vector for antibody production in *Pichia*.

Before turning to the merits of the Office's position, Appellant respectfully submit that the Examiner's Answer mischaracterizes the claimed vector a being exactly the same as pPICZalpha (a vector described in the cited Invitrogen catalog)[1]. The claimed vector is not exactly the same as pPICZalpha. To be specific and explicitly clear: pPICZalpha is a single expression cassette vector whereas the vector recited in the instant claims is a dual expression cassette vector.

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[1] EA Page 8, lines 6-8 ".....would have motivation to use the Pichia strain as well as the expression vectors described in the Invitrogen catalog such as pPICZalpha (which is the exact vector that appellants used) for the

While the arguments below focus upon the combination of the Horwitz, Cregg, Invitrogen Catalog, and Robinson references, it is Appellant's position (as detailed in Appellant's earlier Appeal Brief) that the additional reference of Vanderlaan does nothing to cure the deficiencies of the rejection. The arguments set out below thus apply with equal force to the rejection based on a combination of these references with Vanderlaan.

Appellant now turns to address the position of the Office as set forth in the Examiner's Answer.

The Office has provided no factual evidence to rebut Appellant's evidence that "yeast" in the context of Robinson is limited to S. cerevisiae

Appellants respectfully submit that **at no point does Robinson provide any guidance as to what is meant by "yeast".** In order to determine what the meaning of "yeast" is in Robinson, one must consider what meaning the term would be given by one or ordinary skill in the art upon reading Robinson's disclosure. See, e.g., MPEP 2141.02.[2]

To this end, Appellant has submitted the Declaration by Dr. James Trager (abbreviated hereafter as "TD"). The Trager Declaration is evidentiary support for Appellant's position that "yeast" as used in the context of Robinson solely refers to the species of *Saccharomyces cerevisiae*, and not a genus of fungi that might encompass *Pichia.* Dr. Trager's reasoning for this position is set forth in TD ¶¶11-12. Any suggestion by Robinson to use a dual expression cassette to express an antibody in yeast is, therefore, a suggestion to use a dual expression

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expression of the antibody because..."

[2] MPEP at §2141.02: "A prior art reference must be considered in its entirety, i.e., as a whole, including portions

cassette vector to express an antibody in *S. cerevisiae, not in a genus that might encompass Pichia*. TD ¶13

The Office has provided no evidence to the contrary to rebut this conclusion by the Trager Declaration.

Instead, the Office's response to the evidence of the Trager Declaration has been, for example:

> In response to this argument, the term "yeast" can encompass Pichia and in fact does and one reading the art of the invitrogen catalog or the Cregg reference in combination with the cited references would have motivation to use the Pichia strain as well as the expression vectors described in the Invitrogen catalog such as pPICZalpha (which is the exact vector that appellant's used) for the expression of the antibody because of the benefits recited for the Pichia expression system catalog or in the Cregg et al reference.

Examiner's Answer, page 8.

With all due respect, this is an wholly unsupported assertion by the Office. Further, the Office has apparently dismissed the Trager Declaration out of hand, in contradiction to the law. Under the case law and its own rules of practice, the Office is required to consider the factual evidence in the record, including the Trager Declaration and its factual underpinnings, and either accept them as true or rebut them with a factual showing of its own. *In re Alton*, 76 F.3d 1168,

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that would lead away from the claimed invention." [emphasis in the original].

1175, 37 U.S.P.Q.2d (BNA) 1578, 1583 (Fed. Cir. 1996). With all due respect, the Office has failed to provide any such factual showing.

Appellants respectfully submit that the Office's argument becomes untenable if the term "yeast", as used in Robinson, is interpreted to mean *S. cerevisiae*, not a genus of fungi that includes *Pichia*. The Office's position *requires* that the term "yeast", as used in Robinson, means a genus of fungal species that encompasses *Pichia*. Moreover, *Robinson itself does not show that such a dual expression cassette would work in S. cerevisiae for production of a functional antibody.* Thus, there are two leaps made by the Office in arguing that there is sufficient motivation to apply the disclosure of Robinson to *Pichia*:

1) that Robinson's simple disclosure – unsupported by data – of a dual expression cassette for antibody production in *S. cerevisiae* is sufficient to provide an enabling disclosure requisite for Robinson to serve as a reference in this regard under the statute; and

2) Robinson's simple disclosure – unsupported by data – of a dual expression cassette for antibody production in *S. cerevisiae* can be readily extrapolated to use in *Pichia*, which is of both a different genus *and* a different taxonomic family.

Since a factual analysis of Robinson's disclosure demonstrates that the term "yeast" is used in Robinson to mean *S. cerevisiae*, not the genus of fungi argued by the Office, the Appellants respectfully submit that that the Office's argument lacks force. Interpreting the word "yeast" to mean *S. cerevisiae* in Robinson, a *prima facie* case of obviousness cannot be established because one of skill in the art would find no motivation to produce an antibody in *Pichia* using a dual expression cassette vector.

This rejection may be withdrawn on this basis alone.

The combined references fail to provide a reasonable expectation of success

Further, the Appellants have repeatedly argued that one of skill in the art would not practice the invention with any reasonable expectation of success. As set forth in great detail in the Appellant's Brief, factual support for the Appellants arguments is found in at least three sources:

a) Pennell -- a review of protein expression in *Pichia* that states that there are no reports of proteins greater than 117 kDa being expressed in P. pastoris;

b) Holliger -- a review of antibody expression in *Pichia* that explicitly states that dual expression cassette vectors should be avoided for antibody expression in *Pichia*; and

T) the Trager Declaration -- In this Declaration, Dr. Trager swears, under penalty of Section 1001 of Title XVIII of the United States Code, that one of skill in the art would have no reasonable expectation of success in producing an antibody in *Pichia* using a dual expression cassette vector.

The Office has ostensibly considered each of these pieces of evidence provided by Appellant and summarily dismissed their evidentiary weight. Appellant's respectfully submit that the Office has erred.

Pennell

In the Examiner's Answer, the Office dismissed the teachings of Pennell because the Office has identified one protein of greater than 117 kDa (i.e., GP-120, of 120 kDa) that can be expressed in *Pichia*. Further the Office has attempted to dismiss Pennell's teachings Pennell does

not explicitly state that antibodies cannot be produced in *Pichia*. The Appellants respectfully submit that one exception to Pennell's general teaching does not cause Pennell's teaching to fall flat. Even with one exception, one of skill in the art would still look towards Pennell for guidance as to which system to use for antibody expression in *Pichia,* and note that Pennell in general teaches away from using *Pichia* to produce proteins of greater than 117 kDa. Since heavy and light chain-containing antibodies are larger than 117 kDa (e.g., a full length human antibody is approximately 150 kDa) one of skill in the art would be led away from using *Pichia* to produce an antibody. Accordingly, even in light of this single exception, Pennell still teaches away from the claimed invention.

Holliger

Holliger explicitly states that dual expression cassette vectors should be avoided for antibody expression in *Pichia*. The Office has dismissed the teachings of Holliger solely because Holliger was published *after* the filing date of the instant application. Specifically, the Office stated:

> The Brief on page 13 argues that Holliger teaches that two chain antibody formats require that the two chains be cloned and transformed separately, therefore, single expression cassettes are required if expression of two different chains of an antibody is desired. It is noted that the Holliger reference was published in 2002 and would not have been available as prior art at the time the claimed invention was made. As such the skilled artisan would not have considered it because it was not available and is a moot point in this Brief.

Examiner's Answer page 9.

The Office also states:

> The Brief argues on page 15-16 that the examiner finds appellant's arguments regarding the teachings of Holliger unconvincing and rebuts this by saying Dr. Trager states that in no uncertainty Holliger directs one away from the invention. In response to this argument, again the Holliger reference would not have been available to the skilled artisan at the time of the invention and the argument is moot.

(Examiner's Answer, page 11)

The fact that Holliger was published *after* the instant filing date (in fact, almost three years after the instant filing date) only serves to *strengthen* the Appellants' arguments. Holliger provides evidence that even as late as 2002, those of skill in the art indicated that production of antibodies having two chains *requires* that the two chains be cloned and transformed separately in *Pichia.* If those of skill in the art as late as *2002* taught that a dual expression cassette vector could not be used to express an antibody in *Pichia*, it follows that the same must have been true in 1999, the year of filing of the instant application.

In fact, the view in the art with regard to antibody production in *Pichia* in 1999 could only have been more negative than the prevailing opinion of 2002 since systems for producing proteins in *Pichia* in 2002 had presumably improved and been advanced between 1999 and 2002.

In order to sustain it's position, does the Office argue that those of ordinary skill in the art in 1999 had a reasonable expectation of success of practicing a dual expression cassette for antibody expression in *Pichia*, but that those of ordinary skill in the art in 2002 changed their minds, as evidenced by Holliger? And if this is the case, doesn't the evidence in 2002 only show

that those ordinarily skilled artisans in 1999 were incorrect as to the reasonable expectation of success in practicing the invention?

Furthermore, Appellant's use of reference published after the filing date of the invention are appropriate. References which do not qualify as prior art because they postdate the claimed invention may be relied upon to show the level of ordinary skill in the art at or around the time the invention was made. *Ex parte Erlich*, 22 USPQ 1463 (Bd. Pat. App. & Inter. 1992) *See also* MPEP § 2124.

Here, while Holliger does not represent prior art in relation to the claimed invention, Holliger's teachings do evidence the non-obviousness of the claimed invention at the time the invention was made and, indeed, even *after the invention was made*.3

The Trager declaration

Finally, the Office has dismissed the Trager declaration because the standard to be used in making a rejection based on obviousness is "a reasonable expectation of success" not "assured success". The Office appears to argue that the standard used by Dr. Trager is "assured success" not "a reasonable expectation of success".

However, quoting directly from paragraph 16 from the Trager declaration: "..... it is my unequivocal opinion that a Skilled Person would have no ***reasonable expectation of success*** in practicing such a method in *Pichia"*. (emphasis added). Dr. Trager refers to "reasonable expectation of success" not "assured success" in his declaration, and, accordingly, the correct

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[3] Appellant's note that Holliger was likely unaware of the current invention, since 1) it was not the subject of a post-filing publication (e.g., a published US, PCT, or foreign application); and 2) it appears to be not the subject of a public disclosure to the scientific community (e.g., by scientific publication or presentation).

standard for non-obviousness is being used. With all due respect, the Office's attempt to dismiss Dr. Trager's testimony is based on error.

In summary, the Office's dismissal of the Appellants arguments lack force. The Appellants maintain their position that the appealed claims are not obvious in view of the cited references. Withdrawal of the current rejections is respectively requested.

SUMMARY

Contrary to the Examiner's assertions, Appellant respectfully submits that the claims are not obvious in view of the cited art for the reasons set forth above, as well as those detailed in the Appeal Brief and during prosecution of the instant application. It is Appellant's position that: a) the cited references provide no motivation or suggestion of a ***dual*** expression cassette vector for antibody production in ***Pichia***; and b) one of ordinary skill in the art would not practice a method of producing antibodies in *Pichia* using a dual expression cassette vector with any reasonable expectation of success in view of the art's teaching directly away from using dual-expression cassette vectors, and because it would not be possible to predict is such a method would work in *Pichia* prior to performing the method.

RELIEF REQUESTED

Appellants respectfully request that the rejections of the pending claims 36-39 and 41-50 under 35 U.S.C. §103 be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Date: July 2, 2004

By: James S Keddie

James S. Keddie

Registration No. 48,920

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, California 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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